

### REMARKS

Claims 1, 2, and 7-14 were pending. Claim 1 is amended herein. Support for the amendment is found throughout the specification, *e.g.*, page 3, lines 19-24. Thus, it is believed that no new matter has been added. Claim 14 is canceled herein. Claims 1, 2, and 7-13 are presently pending. No claim has been allowed.

Applicants gratefully acknowledge the entry of the Preliminary Amendment dated January 15, 2002. Applicants also deeply appreciate the formal granting of the Petition to Make Special filed on January 15, 2002.

#### Priority

The Office requested information regarding as to how Serial No. 09/361,775, now U.S. Patent 6,410,512, differs from 09/113,947, now U.S. Patent No. 6,462,019 to confirm the priority date. Applicants believe that the Examiner has the resources to fulfill his burden to determine priority. Nonetheless, Applicants provide a brief summary of differences between these patents prosecuted and issued by Examiner Gitomer. U.S. Patent No. 6,410,512 has examples relating to the stimulation of hair growth while U.S. Patent No. 6,462,019 has examples relating to the stimulation of bone growth and has disclosure relating to hair growth at, *e.g.*, page 11, lines 20-24 and page 12, line 19 to page 13, line 4.

The Office requested the identity of any related applications, abandoned, pending or allowed. The co-pending, related Application Serial No. 10/050,633, now allowed, contains claims to the stimulation of hair growth with epoxomicin. In the co-pending, related Application Serial No. 10/052,832, the independent claim covers the use of a genus of compounds that inhibit proteasomal activity or that inhibits production of proteasome proteins to stimulate hair growth. Peptidyl aldehydes and peptidyl epoxy ketones are species within this genus. Application Serial Nos. 09/421,545, 09/558,973 (now allowed), and 09/695,807 also are related to the instant application and have claims directed to the stimulation of bone growth using various inhibitors of proteasomal activity.

**Formal Matters**

The Action states that the application fails to comply with the sequence disclosure requirements of §§ 1.821 through 1.925 for one or more reason in the attached form. Applicants note that the referenced attached form was not included in the Action. Nonetheless, the specification is amended herein to include SEQ ID NOs for sequences of four or more amino acids.

The Action dates that the declaration is defective because G. Rossini did not provide a full name. A substitute declaration is included herein as Exhibit A.

The Office asserts that the references submitted are directed towards non-analogous art and suggest that Applicants are trying to “bury” relevant prior art references. Applicants **strenuously object** to this gross mischaracterization of a routine practice in patent prosecution. First, these references include all of the references of the related parent cases. This is a common practice before the Office and, in fact, is required if the Applicant desires the printing of the considered references on the face of the patent. *See* MPEP § 609(I)(A)(2). Applicants desire the printing of all of the references from the parent applications also be printed on the face of the patent. Second, Applicants note that a number of the references relate to proteasomes, their biology, and various inhibitors and other relate to hair biology and growth. The nature of at least these references as analogous art is self-evident from the titles and abstracts of the references. Third, the Examiner has now examined this very set of references in at least four related cases, three of which have been allowed. In two of these cases, claims directed to hair growth have issued without the Examiner asserting that Applicants have buried relevant prior art references. Finally, Applicants note that the Examiner has returned a signed IDS 1449 form indicating his full consideration of the submitted references. Applicants believe it is highly unlikely that the skilled artisan would characterize the references relating to hair biology and growth and proteasomal biology as non-analogous art. Indeed, the absence of references directed to the use of the claimed compounds to stimulate hair growth in the references submitted to date is a reflection of the novelty of the invention. Nonetheless, in an effort to expedite the prosecution of this application, the Applicants point out that at least the following references address hair growth directly: Blessing et al.; Hardy; Lutz; Gupta et al.; Gat et al.; and U.S. Patent Nos. 5,767,152 and 5,824,643. At least the following references address proteasomal

biology: Wojcik, et al.; Wozney et al., Vintitsky et al.; Sin et al.; Peters; Brochmann Murray et al.; Meng et al.; Jensen et al.; Hilt et al.; Groll et al.; Garrett et al.; Figueiredo-Pereira et al.; Eloffson et al.; Craiu et al.; Coux et al.; Baumeister et al.; Adams et al.; WO 95/25533; U.S. Patent Nos. 6,083,903, 5,780,454, and 5,580,854.

### **Objections**

The Office objects to the title the invention as it is allegedly not aptly descriptive. Applicants respectfully submit that the title aptly describes the presently claimed invention.

The Office objects to the Abstract of the Disclosure as it is allegedly not directed to the claimed invention. An amended abstract is provided herein.

The Office objects to the headings and format of the specification as they are allegedly not standard. The specification is amended herein and have provided a substitute specification showing these amendments. A clean copy of a substitute specification and a marked up copy of the substitute specification are provided herein as Exhibits B and C, respectively. No new matter has been added in the substitute specification. For the convenience of the Examiner, the substitute specification also includes the amendments made in the Preliminary Amendment filed January 15, 2002, the amendments of the instant response, as well as paragraph numbers.

The Actions objects to the specification as failing to provide proper antecedent basis for the claimed subject matter, citing 37 C.F.R. § 1.75(d)(1) and MPEP § 608.01(o), because the specification allegedly fails to provide written description for the presently claimed peptidyl aldehyde. Applicants traverse this objection.

Applicants have amended the original specification herein at page 15, line 1 to include the language of the original claim 3, which reads as follows:

3. The method of claim 1 wherein said compound is lactacystin or a peptidyl aldehyde.

Applicants believe that this amendment provides the necessary antecedent basis for the term “peptidyl aldehyde.”

In light of the above remarks, Applicants respectfully submit that the objections to the specification have been overcome. Therefore, Applications request the withdrawal of the objections.

**Rejection Under Judicially Created Doctrine of Obviousness-Type Double Patenting**

Claim 1, 2, and 7-14 are rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 1-8 of U.S. Patent 6,410,512. According to the Action, the conflicting claims are not identical, but they are not patentably distinct from one another.

As no allowable subject matter has been indicated in the instant case, Applicants request that this rejection be held in abeyance until such time. Applicants will submit a terminal disclaimer once allowable subject matter is indicated in the present application if it is required.

**Rejection Under 35 U.S.C. § 112, First Paragraph**

Claim 14 is rejected under 35 U.S.C. § 112, second paragraph as allegedly failing to described EST in a meaningful way. The Action also asserts that EST is not understood as to what compound may be intended in claim 14. Applicants traverse this rejection.

EST is an art-recognized acronym for the compound [2S,3S]-trans-epoxysuccinyl-L-leucylamido-3-methylbutane ethyl ester. However, while EST is a proteasomal inhibitor, it is not a peptidyl epoxy ketone, and was inadvertently included as a peptidyl epoxy ketone in claim 14. Therefore, while Applicants believe that the acronym "EST" conveys the identity of the compound to the skilled artisan, this claim is canceled herein to ensure proper dependency from the pending independent claim, and thus, the rejection is rendered moot.

In view of the above, Applicants respectfully submit that the rejection under 35 U.S.C. § 112, first paragraph has been overcome. Therefore, Applications request the withdrawal of the rejection.

**Rejection Under 35 U.S.C. § 112, Second Paragraph**

Claims 2 and 12-14 are rejected under 35 U.S.C. § 112, second paragraph, as "said compound" allegedly lacks antecedent basis. Applicants traverse this rejection.

Claim 1 is amended herein to provide proper antecedent basis to the term “said compound.”

In view of the above, Applicants respectfully submit that the rejection under 35 U.S.C. § 112, second paragraph has been overcome. Therefore, Applicants request the withdrawal of the rejection.

**Rejections Under 35 U.S.C. § 102(a) and (b)**

Claims 1, 2, and 7-14 are rejected under 35 U.S.C. § 102 (a) as allegedly being anticipated by Bathurst, U.S. Patent No. 6,495,532. According to the Action, Bathurst teaches growth factors and calpain inhibitors that prevent apoptosis. Bathurst also allegedly teaches that hair loss is treated. The Action highlights Bathurst’s disclosure that hair loss can be caused by apoptosis of the cells of the hair follicles, and therefore that the compositions are suitable for use in topical treatment of skin to prevent continued hair loss.

Claims 1, and 7-11 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by each of Miller, WO 96/33268, and Horvitz, WO 93/25694. According to the Action, Miller teaches peptidyl derivatives which are modulators of the activity of pro-apoptotic cysteine proteinases and that they may be used to treat alopecia. The Action asserts that Horvitz teaches peptide aldehydes may be useful for inhibiting cell death and further that conditions characterized by cell death, such as hair loss, may be treated.

Applicants traverse these rejections.

Applicants respectfully submit neither Bathurst, Miller, nor Horvitz teaches all of the features of the claims. *See* MPEP § 2131 (“A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.” (citations omitted) (emphasis added)). None of these references satisfies the anticipation standard.

Bathurst fails to anticipate the instant claims because this reference fails to teach each and every element of the claimed methods. Bathurst relates to therapeutic compositions containing lysophosphotidic acids (LPA), methods for making such compositions, and methods of using the compositions in the preservation and treatment of organs. Bathurst does not disclose or suggest the use of proteasomal inhibitors to stimulate hair growth for at least the following reasons. To

Applicants' knowledge, LPA is not a proteasomal inhibitor. Moreover, Bathurst is completely silent regarding the use of proteasomal inhibitors. The passage cited by the Examiner regarding growth factors and calpain inhibitors at column 3 of Bathurst provides no additional guidance or teaching regarding the use of proteasomal inhibitors. In fact, Bathurst contains no disclosure regarding the stimulation of hair growth. The Examiner cites to two passages that disclose the use of LPA to treat hair loss and the mechanism of hair loss as potentially being apoptosis. It appears that the Examiner is equating the inhibition of apoptosis, *i.e.*, cell death, with the stimulation of the opposing process, cell growth. However, there is no suggestion in the cited references that the inhibition of cell death will necessarily result in cell growth. Moreover, the stage of hair follicle life cycle associated with hair loss, *i.e.*, catagen, is recognized in the art as a separate stage of the hair follicle life cycle. For example, the publication cited by Bathurst (see last full paragraph of column 40) states:

The hair follicle undergoes a cycle of growing, regressing, and resting phases (anagen, catagen, telogen, respectively). As the follicle enters catagen, the cells of the lower, cycling portion undergo a process of controlled cell death (apoptosis).

See Exhibit D, abstract. This confirms other statements made in the art such as that found in a reference previously cited by Applicants. See *e.g.*, Hardy, *Trends in Genetics* 8:55-61 (1992) (stating that "hair growth is cyclic, with every hair follicle proceeding from an active phase (anagen) through a regressive and shortening phase (catagen) to a resting phase (telogen)"). Thus, cells can avoid cell death during catagen and remain viable without any stimulation of cell growth whatsoever. Bathurst contains no disclosure regarding the use of any compounds to stimulate the anagen cycle of the hair follicle. Thus, in the complete absence of any teaching regarding proteasomal inhibitors and any teaching using such compounds to stimulate hair growth, Bathurst fails to anticipate the instant methods.

Miller lacks the teaching of each and every element of the claimed methods. Miller relates to the identification and isolation of the enzyme, apopain, also known as caspase 3, YAMA, and CCP-32, and its use and the use of its inhibitors in immune, proliferative, and degenerative diseases, including alopecia. First, Miller is completely silent regarding inhibitors of proteasomal activity. The inhibitors disclosed by Miller are inhibitors of an enzyme, *i.e.*, caspase, that cleaves PARP and

is a critical player in the induction of apoptosis. Second, there is no disclosure regarding the stimulation of the growth of any cell. Like Bathurst, Miller is directed to the inhibition of unwanted apoptosis. The absence of apoptosis does not necessarily correlate with the stimulation of cell growth. Thus, even if a peptidyl aldehyde useful in inhibiting apopain also inhibited proteasomal activity, there is a complete lack of teaching regarding the use of such an inhibitor to stimulate hair growth. The teaching regarding the treatment of alopecia does not cure this deficiency. Miller discloses the treatment of alopecia using inhibitors of apopain to inhibit inappropriate cell death (*i.e.*, apoptosis) but not to stimulate cell growth. Again, the absence of apoptosis alone does not necessarily correspond with the stimulation of hair growth. Hence, Miller fails to teach the use of proteasomal inhibitors that are peptidyl aldehydes or peptidyl epoxy ketone to stimulate of hair growth and therefore does not anticipate the instant methods.

Horvitz also fails to teach each and every element of the claimed methods. Horvitz relates to the identification and characterization of human interleukin- $\beta$  convertase (ICE) and the use of its inhibitors/modulators to treat diseases and conditions characterized by cell death including alopecia. Again, peptidyl aldehydes are disclosed only as inhibitors of cell death. Horvitz lacks any disclosure regarding the inhibition of proteasomal activity or the use of such inhibitors to stimulate hair growth. In fact, the drugs, *e.g.*, inhibitors, disclosed by Horvitz are those that inhibit the production of IL-1 $\beta$  and apoptosis. *See* page 9, lines 1-12. Thus, Horvitz fails to disclose proteasomal inhibitors or the use of such inhibitors as stimulators of hair growth and therefore does not anticipate the claimed methods.

Each of these references lacks multiple features of the claimed methods. Not one of these references even suggests the use of the disclosed compounds for the stimulation of cell proliferation or more specifically, hair growth. Thus, for at least these reasons, none of these references anticipate the claimed methods.

In view of the above, Applicants respectfully submit that the rejection under 35 U.S.C. §§ 102(a) and (b) has been overcome. Therefore, Applications request the withdrawal of the rejection.

### CONCLUSION

Applicants submit that the objections and the rejections under 35 U.S.C. §§ 102 (a), 102 (b), and 112, second paragraph have been overcome by the above remarks. Early allowance of the remaining pending claims 1, 2, and 7-13 is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 432722002601. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: March 8, 2004

Respectfully submitted,

By

  
Laurie L. Hill, Ph.D.

Registration No.: 51,804

MORRISON & FOERSTER LLP

3811 Valley Centre Drive, Suite 500

San Diego, California 92130

(858) 720-7955